JACC: ASIA VOL. 3, NO. 5, 2023

CLINICAL RECOMMENDATIONS ON ASIAN POPULATIONS

Practical Application of Coronary Physiologic Assessment

Asia-Pacific Expert Consensus Document: Part 1

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ABSTRACT

Coronary physiologic assessment is performed to measure coronary pressure, flow, and resistance or their surrogates to enable the selection of appropriate management strategy and its optimization for patients with coronary artery disease. The value of physiologic assessment is supported by a large body of evidence that has led to major recommendations in clinical practice guidelines. This expert consensus document aims to convey practical and balanced recommendations and future perspectives for coronary physiologic assessment for physicians and patients in the Asia-Pacific region based on updated information in the field that including both wire- and image-based physiologic assessment. This is Part 1 of the whole consensus document, which describes the general concept of coronary physiology, as well as practical information on the clinical application of physiologic indices and novel image-based physiologic assessment.

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ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2023.07.003

JACC: ASIA, VOL. 3, NO. 5, 2023
OCTOBER 2023:689–706

ABBREVIATIONS AND ACRONYMS

CFC = coronary flow capacity

CFR = coronary flow reserve

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

IMR = index of microcirculatory resistance

IVUS = intravascular ultrasound

MI = myocardial infarction

NHPR = nonhyperemic pressure ratio

PCI = percutaneous coronary intervention

QFR = quantitative flow ratio

From a broad perspective, coronary physiologic assessment can be defined as the use of diagnostic indexes derived from coronary pressure and flow, either measured directly in the coronary vessels or derived from image-based computational fluid dynamics, to investigate the presence of obstructive and nonobstructive causes of myocardial ischemia. The aim of the physiologic assessment is to enable cardiologists to select the best management strategy for patients with coronary artery disease. The history of invasive coronary physiologic assessment has developed in tandem with interventional cardiology, with significant developments over the last 2 decades and the accumulation of supporting clinical data. Despite the fact that invasive physiologic assessment is now strongly recommended in all practice guidelines, its adoption in daily practice generally remains low both globally and in the Asia-Pacific region.[1-3]

With the aim of conveying practical and balanced recommendations and future perspectives for coronary physiologic assessment, *JACC: Asia* promoted the drafting of an expert consensus document that could serve as a reference document for physicians in the Asia-Pacific region and ultimately favor the adoption of these diagnostic tools. A working group made of experts in this field carefully reviewed past and new data to provide practical and balanced recommendations and future perspectives for coronary physiologic assessment. The value of new image-based physiologic assessment has been considered along well-established wire-based approaches. In addition, attention has been paid to analyzing recent studies in the field of coronary physiology whose results may contradict previous ones.[4] During this process, the working group has collected data from the Asia-Pacific region as much as possible to make practical and clinically useful recommendations for physician and patients in this area. Details of working group members, including their potential conflict of interest, are presented in Supplemental Appendix.

It is hoped that this document will guide physicians to understand the coronary physiologic status and physiologic backgrounds of patients' disease and make the appropriate coronary physiologic assessment and treatment decision-making for patients with coronary artery disease in daily practice.

INVASIVE PHYSIOLOGIC ASSESSMENT

HISTORY. Invasive physiologic assessment of coronary artery disease was attempted from the beginning of coronary angioplasty.[5] In the early period of coronary angioplasty, the pressure gradient across the lesion was measured to assess the severity of stenoses and the results of the angioplasty. Andreas Gruentzig used the translesional pressure gradient after balloon dilation as a metric of procedural success. However, this methodology could not be extended to pre-procedural assessment due to the use of thick over-the-wire balloon catheters, which caused an overestimation of the pressure gradient across the stenosis. The development of thin coronary guidewires equipped with a sensor to measure flow velocity, pressure, or temperature expanded the knowledge of the coronary circulatory system and enabled invasive coronary physiologic assessment in the clinical field.[6-8] Over the last few decades, several physiologic indexes have been developed based on coronary pressure, flow or its velocity, or both (**Table 1**).[9-16] With these indexes, operators can assess the physiologic status of the entire coronary circulatory system, from the epicardial coronary arteries to the microcirculation in patients with suspected ischemic heart disease. Many randomized trials and large-scale registries have shown the benefit of incorporating invasive coronary physiology into clinical practice and contributed to accumulating basic and practical knowledge on the coronary circulatory system.[17-21] Consequently, the latest guidelines recommend the use of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) as a Class Ia recommendation to assess epicardial coronary stenosis and also recommend coronary flow reserve (CFR) or index of microcirculatory resistance (IMR) as Class IIa recommendation for the assessment of microvascular diseases.[22-25]

SET-UP AND PITFALLS IN CORONARY PRESSURE MEASUREMENTS. Intracoronary pressure measurements should begin with calibration and equalization of both a pressure wire and a fluid-filled pressure

Kentaro Hayashida, MD, PhD, served as Guest Associate Editor for this paper. Nathan Wong, PhD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 5, 2023; revised manuscript received June 13, 2023, accepted July 8, 2023.

TABLE 1 Invasive Physiologic Indexes Used in Daily Practice

Physiologic Index	Definition	Cut-Off Value	Features
Fractional flow reserve (FFR)	Ratio of distal coronary pressure to aortic pressure in hyperemic status	≤0.80	Epicardial coronary artery specific index Reflecting maximal flow limitation due to epicardial coronary artery disease Extensive clinical data
Instantaneous wave-free ratio (iFR)	Ratio of distal coronary pressure to aortic pressure during the diastolic wave-free period in resting status	≤0.89	Epicardial coronary artery specific index No need of hyperemia Noninferior outcome to FFR-guided revascularization
Resting full cycle ratio (RFR)	Lowest value of the ratio of distal coronary pressure to aortic pressure in resting status	≤0.89	Epicardial coronary artery specific index No need of hyperemia High degree correlation and agreement with iFR
Diastolic pressure ratio (dPR)	Average ratio of distal coronary pressure to aortic pressure during the diastolic period in resting status	≤0.89	Epicardial coronary artery specific index No need of hyperemia High degree correlation and agreement with iFR
Coronary flow reserve (CFR)	Ratio of hyperemic coronary flow and resting coronary flow	<2.0-2.5	Reflects both epicardial coronary artery disease and microvascular dysfunction Influenced by various factors, such as hemodynamics, conditions, or contractility Enormous data regarding its prognostic value
Coronary flow capacity (CFC)	Combination of coronary flow reserve and coronary stress flow	CFR <1.74 and coronary stress flow <1.12 mL/min/g[a]	Reflects comprehensive coronary physiologic status Less influenced by resting flow conditions
Index of microcirculatory resistance (IMR)	Distal coronary artery pressure multiplied by hyperemic mean transit time	> 25 U	Microcirculation-specific index Proven prognostic value in many studies
Hyperemic microvascular resistance (hMR)	Ratio of maximal coronary flow velocity to distal coronary artery pressure during hyperemia	> 2.5 mm Hg/cm/s	Microcirculation-specific index Relatively few outcome data

[a]The cut-off values for discriminating severely reduced CFC from cardiac positron emission tomography study. In the invasive physiologic assessment, the cut-off values of 1.7 for CFR and 26 cm/s for hyperemic average peak velocity are used.

monitoring system (Figure 1). With the fluid-filled pressure transducer located at the height of a patient's heart, the zero-reference is taken manually or automatically when the wire is connected to a console. After the calibration of the pressure wire, the wire is advanced until the pressure sensor comes to be aligned with the tip of the guiding catheter. Generally, the size of a catheter does not significantly influence the results of coronary physiologic assessment, except for a higher chance of coronary pressure damping when using large catheters. The guiding catheter system should then be flushed with saline, and the pressures of the catheter and the pressure-wire are equalized. During the equalization process, the mean pressures, waveforms, and temporal alignments must be equalized. If they cannot be equalized properly, the whole fluid-filled system needs to be repeatedly flushed with saline to remove microbubbles or contrast medium. It is important to take out the wire introducer from the Y connector and disengage the guiding catheter to avoid pressure damping during equalization and pressure measurements.

After equalization, the pressure wire is advanced into the coronary artery of interest, and the pressure sensor should be positioned within the distal one-third of the target vessel. When it is difficult to advance the wire distally, it may be acceptable to place the pressure sensor at least 2 to 3 cm distal to the target lesion to avoid wire-induced injury or accordion effect. Before the pressure measurement, gentle disengagement of a guiding catheter is needed to avoid pressure damping, even in cases without the ostial lesion. During pressure measurements, the operators need to check the aortic and distal coronary pressure waveforms to detect possible measurement errors from contrast medium, pressure drift, aortic pressure damping, and whipping noise. For FFR and nonhyperemic pressure ratios (NHPRs), the full hyperemic and resting conditions should be ensured, respectively. Hyperemia can be induced by intravenous adenosine or adenosine triphosphate, intracoronary nicorandil, papaverine, or intracoronary adenosine (Table 2).[26]

After measurement of FFR or NHPR, a pullback pressure tracing should be performed to disclose the physiologic lesion distribution, including its pattern, and to check the pressure drift. For drift check, it is practical to evaluate the drift at the tip of a guiding catheter using the same index used for disease assessment. If a drift of more than 0.02 U or 0.03 U is observed, the above-mentioned procedures must be repeated after the re-equalization of a pressure wire. As the guiding catheter can easily advance while

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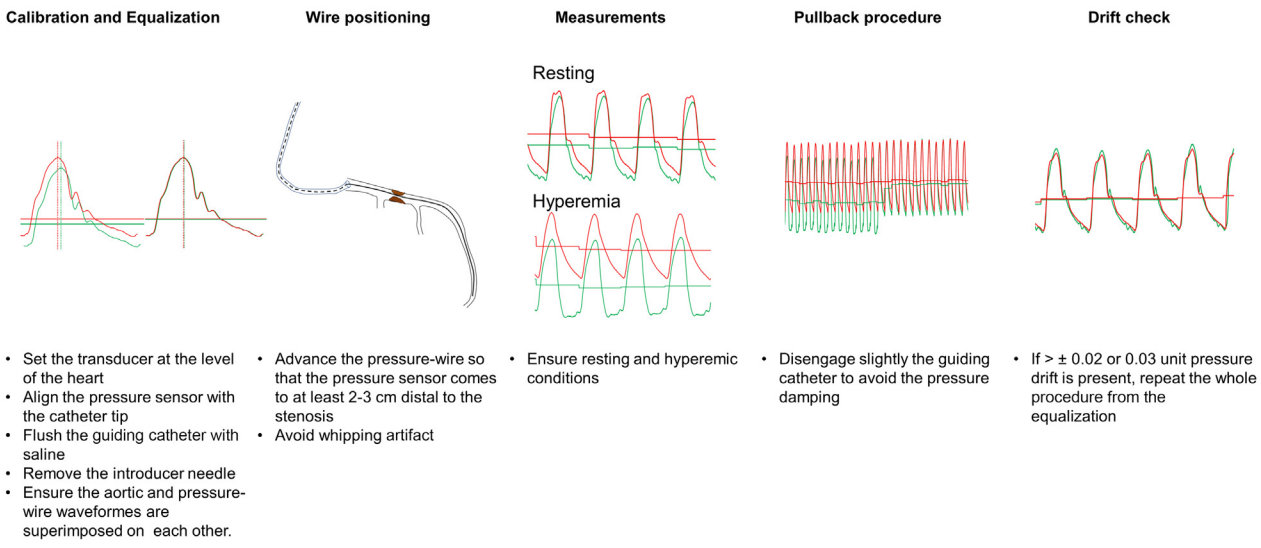
FIGURE 1 Procedural Steps of Intracoronary Pressure Measurements



Intracoronary pressure measurement is performed through the process of calibration, equalization, wire positioning, nonhyperemic pressure ratio/fractional flow reserve measurements, pullback procedure, and drift check.

pulling back the pressure wire, operators should intentionally maintain gentle tension on the guiding catheter to avoid pressure damping throughout the pullback procedure.

SET-UP AND PITFALLS IN CORONARY FLOW MEASUREMENTS. Coronary flow velocity can be measured by a guidewire equipped with a Doppler sensor at its tip (Figure 2). The Doppler sensor has a sample volume about 5 mm distal to the wire tip. The sensor emits and receives pulsed ultrasound waves and can measure the velocity of blood cells traveling within the sample volume. The Doppler-sensor wire can be used without manual calibration and equalization. The most important technical issue while using the Doppler-sensor wire is adequate positioning of the wire tip to obtain appropriate Doppler signals. The wire tip needs to be manipulated to set the sample volume within the midstream of blood flow so that clear phasic systolic and diastolic Doppler signals are recorded without noise. For the hemodynamic assessment of a stenotic lesion, the sensor should be positioned at least 2 cm distal to the stenosis where laminar flow is re-established. Another way to assess coronary flow is a thermodilution method using a pressure-temperature sensor wire (Figure 2).[27,28] In this wire, the temperature sensor sitting together with the pressure sensor serves as the distal thermistor, and that at the shaft of the wire serves as the proximal thermistor. These 2 thermistors can record changes in temperature over time when an indicator, which is generally saline, is given, and the transit time of saline from the proximal to the distal thermistor can be used as a proxy of the flow. To measure the mean transit time in a coronary artery, the distal thermistor should be located at the distal third part of the vessel, and then, 3 to 4 mL of saline is injected into the vessel through the catheter 3 times. During this injection, a guiding catheter should be securely positioned inside the coronary artery. The reciprocal of the mean transit time (1 / mean transit time) is considered a surrogate marker for blood flow. The CFR is calculated as the ratio of 1 / mean transit time during hyperemia to that during the resting state. The IMR is calculated as the distal pressure of the epicardial coronary artery divided by 1 / mean transit time during hyperemia.

FLOW-BASED PHYSIOLOGIC ASSESSMENT

The primary goal of coronary revascularization is to improve myocardial perfusion by removing flow-limiting stenosis. Therefore, it is crucial to evaluate coronary flow and its determinants in patients with coronary artery disease. Coronary flow-based physiologic indices such as CFR have been shown to have a strong predictive value for adverse cardiac events in patients with ischemic heart disease.[29-31] For

TABLE 2 Characteristics of Commonly Used Hyperemic Agents

Agents	Route	Dose	Effect Time	Side Effect	Comment
Adenosine	Intravenous	140 μg/kg/min	During administration	Chest discomfort Bronchospasm Hypotension Transient AV block	Gold standard method Stable steady-state hyperemia
Adenosine	Intracoronary	LCA: 200 μg RCA: 100 μg	5 to 15 s	Transient AV block	Inappropriate for pullback tracing Possibility of suboptimal hyperemia
Nicorandil	Intracoronary	2 mg	15 to 30 s	Rare VF	Safe and quick No significant side effects
Regadenoson	Intravenous	400 μg	2 to 3 min	Chest discomfort Headache Risk of seizure	Quick response with sufficient effect Less bronchospasm, AV block, hypotension
Papaverine	Intracoronary	LCA: 12 mg RCA: 8 mg	30 to 60 s	QT prolongation Hypotension, ventricular arrhythmia	Rare fatal ventricular arrhythmia

AV = atrioventricular; LCA = left coronary artery; RCA = right coronary artery; VF = ventricular fibrillation.

noninvasive assessment, positron emission tomography, using [^{15}O]H_2O, rubidium-82, or ^{13}N-ammonia as flow tracers, has remained the standard mode for quantifying myocardial blood flow.[29,30,32] Invasively, coronary flow and its surrogates can be measured using a pressure-temperature sensor-tipped wire or Doppler-sensor wire. The thermodilution method using a pressure-temperature sensor wire has become a more popular method of coronary flow assessment in catheterization laboratories due to its widespread availability.[33] CFR has been reported as one of the most important predictors of clinical outcomes in patients with coronary artery disease. IMR is a specific index of microvascular dysfunction that may affect FFR values.[34] Lee et al[35,36] reported that low CFR and high IMR were associated with an increased risk of adverse clinical outcomes such as death and myocardial infarction (MI).[35,36] High IMR (>40) of the infarct-related artery after successful percutaneous coronary intervention (PCI) for acute MI is an independent predictor of adverse cardiac events.[37,38]

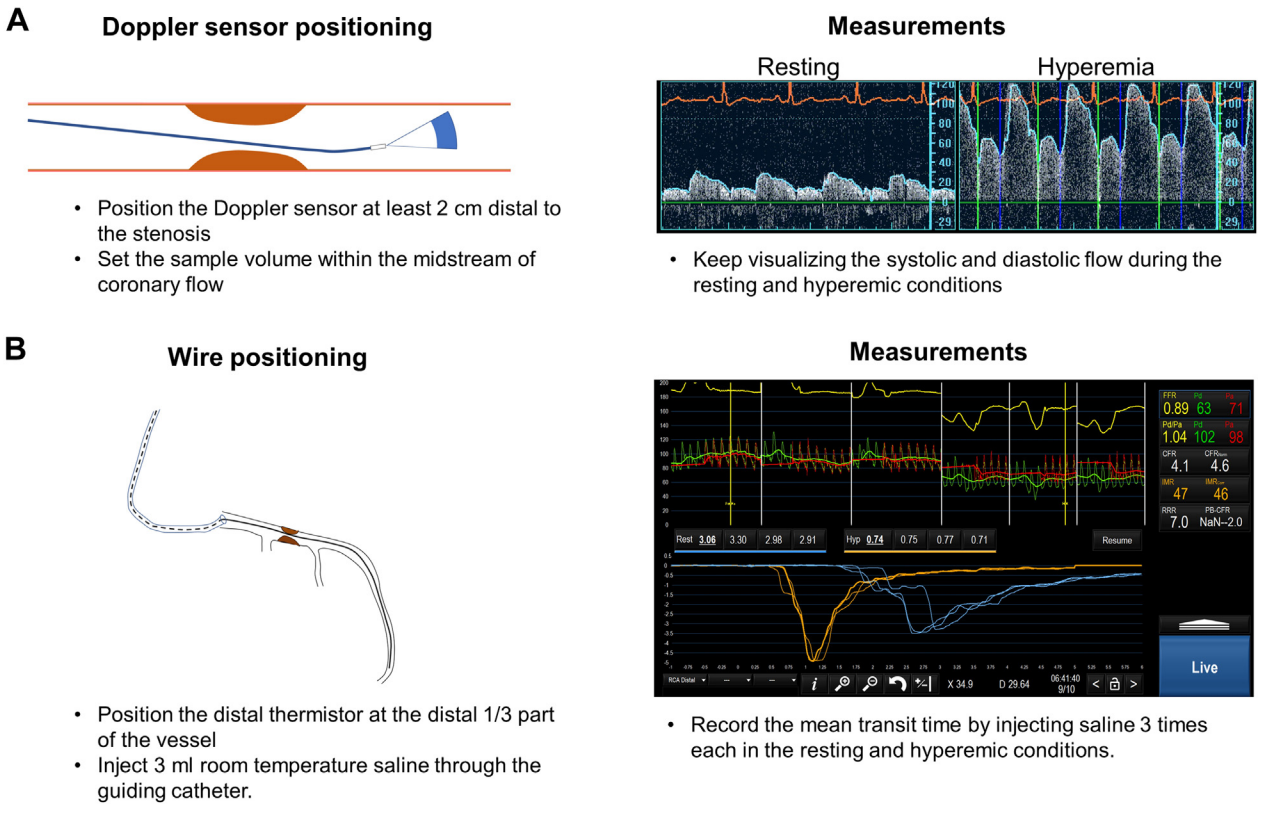
A Doppler-sensor wire can measure coronary flow velocity at the point where the sensor is located. The ratio of average peak velocity during hyperemia to baseline is defined as the coronary flow velocity reserve. A guidewire with a pressure sensor and Doppler crystal allows simultaneous measurement of pressure and average peak velocity at the wire tip, which provides a reliable surrogate index of microvascular resistance (hyperemic microvascular resistance).[39] In comparison with the thermodilution method, Doppler-derived CFR showed a better correlation with ^{15}H-H_2O positron emission tomography–derived CFR.[40] Although CFR is a well-known prognostic indicator in a wide spectrum of patients, one pitfall of this index is its dependency on resting conditions. Coronary flow capacity (CFC) is an alternative concept that integrates CFR and maximal hyperemic coronary flow and provides a comprehensive assessment of coronary flow characteristics.[14,16,41] Lesions are categorized into normal CFC, mildly reduced CFC, moderately reduced CFC, and severely reduced CFC, according to the combination of the thresholds of flow reserve and hyperemic flow. CFC was reported to have incremental prognostic value to CFR in vessels where revascularization was deferred.[14]

CORONARY PHYSIOLOGY IN TREATMENT DECISION

The most common indication for using physiologic indexes in daily practice is to identify ischemia-causing coronary stenosis and guide for revascularization. Pressure-derived physiologic indexes such as FFR and NHPR are recommended as the standard methods for the revascularization decision-making process in patients with intermediate lesions or without definite evidence for lesion-based ischemia.

FFR-GUIDED REVASCULARIZATION. The value of FFR in the decision process discussed above is supported by several major randomized clinical trials. In the DEFER study (FFR to Determine Appropriateness of Angioplasty in Moderate Coronary Stenoses), 325 patients were assigned to 3 groups (if FFR ≥0.75, the deferral group [n = 91, medical therapy] or the PCI group [n = 90, PCI]; if FFR<0.75, the reference group [n = 144, PCI]) and clinical outcomes were assessed. The 5-year event rates of death or MI were 3.3% in the deferral group and 7.9% in the PCI group, respectively (P = 0.21). The annual risk of cardiac death or MI in patients with high FFR (>0.75) was <1% per year and was not reduced by PCI, suggesting that coronary intervention of functionally insignificant coronary stenosis, regardless of angiographic stenosis, could be

FIGURE 2 Practical Points in Coronary Flow Measurements



Coronary flow can be assessed using a guidewire equipped with Doppler sensor (A) or a pressure-temperature sensor (B).

safely deferred for up to 5 years.[42] Subsequent 15-year follow-up data showed consistent results.[19] From the 2-year clinical outcomes of the FAME study (FFR versus Angiography for Multivessel Evaluation), patients with deferred lesions in the FFR-guided group experienced an incidence of 2.0% of MI and 3.2% of repeat revascularization.[43] In addition, 5-year follow-up outcomes of functionally insignificant (FFR >0.80) proximal left anterior descending artery stenosis were reported to be similar to age- and sex-matched control populations.[44] These studies support the safety of revascularization deferral in epicardial stenoses with nonischemic FFR values. They also showed that stent implantation in functionally insignificant lesions could increase the risk of stent-related events to levels exceeding the risk associated with the deferral of revascularization. Although FFR-guided deferral is generally acceptable, hemodialysis patients who undergo deferral have a 2 to 4 times higher risk of clinical events than non-hemodialysis patients.[45,46] Therefore, they require more intensive medical management and meticulous follow-up.

Although the above-discussed studies support the value of FFR in avoiding unneeded PCI, other trials support the value of an FFR-guided PCI strategy. The FAME II trial (Fractional Flow Reserve-Guided Percutaneous Coronary Intervention Plus Optimal Medical Treatment Versus Optimal Medical Treatment Alone in Patients With Stable Coronary Artery Disease) compared the clinical outcomes of PCI and optimal medical treatment in patients with low FFR (≤0.80).[47] At 5 years, the rate of the primary endpoint of the composite of all-cause death, MI, and urgent revascularization was significantly higher in the medical treatment group.[18] In addition, individual patient data meta-analysis from FAME 2, DANAMI-3-PRIMULTI (Primary PCI in Patients With ST-elevation Myocardial Infarction and Multivessel Disease: Treatment of Culprit Lesion Only or Complete Revascularization), and Compare-Acute (Fractional Flow Reserve Guided Primary Multivessel

Percutaneous Coronary Intervention to Improve Guideline Indexed Actual Standard of Care for Treatment of ST-elevation Myocardial Infarction in Patients With Multivessel Coronary Disease) trials showed that the risk of death or MI was significantly lower in the FFR-guided PCI group than in the medical treatment group.[48] All these data strongly support the revascularization of low FFR lesions. However, these results should be interpreted in the context of the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), which showed that the initial invasive strategy (coronary revascularization) did not reduce the risk of death from any cause compared with the initial conservative strategy (medical treatment) in patients with at least moderate myocardial ischemic burden.[4] In the era of post-ISCHEMIA trial, low FFR or NHPR may be the minimal requirement for revascularization being justified because at least urgent repeat revascularization or spontaneous MI could be reduced by coronary stenting in such situations.

OUTCOME-BASED FFR THRESHOLD FOR REVASCULARIZATION. Notwithstanding the value of fixed FFR cutoffs used for decision-making in the clinical trials discussed above, there is ample evidence suggesting that FFR values depict a continuum of atherosclerotic disease burden that has prognostic implications. The threshold value of FFR for myocardial ischemia was initially validated against noninvasive functional tests. The large prospective IRIS-FFR (A Multicenter, Prospective Cohort to Evaluate the Natural History of FFR Guided Percutaneous Coronary Intervention) registry enrolled 5,846 patients and evaluated the outcome-derived FFR threshold for revascularization in clinical practice.[49] For deferred lesions, the risk of major adverse cardiac events showed a significant, inverse relationship with FFR (adjusted HR: 1.06; 95% CI: 1.05-1.08; $P < 0.001$). However, this relationship was not observed in revascularized lesions. Regression analysis showed that an FFR threshold of 0.79 was associated with major adverse clinical events and an FFR threshold of 0.64 with cardiac death and MI. These results suggested that FFR could be considered a clinical prognostic index in the decision for revascularization as well as a physiologic surrogate for myocardial ischemia.

NONHYPEREMIC PRESSURE RATIOS. The use of adenosine-free NHPRs has been proposed as a simpler and symptom-free alternative to FFR interrogation to make decisions on coronary revascularization. Two randomized controlled trials showed that iFR was noninferior to FFR for guiding revascularization in patients with intermediate stenosis.[20,21] Recently, the 5-year follow-up of the iFR SWEDEHEART (The Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome) trial showed that there was no difference between iFR-guided vs FFR-guided PCI strategies for the 5-year composite outcome of death, MI, and unplanned revascularization.[50] These results support recent guidelines that recommend using either FFR or iFR to guide clinical decision-making for revascularization. Many different NHPRs are now commercially available, and the study results showed that all NHPRs have equal diagnostic accuracy for FFR, the same cutoff value (≤0.89), and similar prognostic impact in cases of deferral of PCI based on NHPRs.[51-53] When both FFR and NHPR are measured in the same lesion, discordant results between FFR and NHPR are reported in approximately 20% of cases. Importantly, discordant lesions with negative NHPR (>0.89) but positive FFR (≤0.80) are more common in the left main and proximal lesion locations. Focal and diffuse patterns of obstructive epicardial disease also account for FFR and iFR discordance.[54] Discordance between FFR and NHPR can occur due to measuring the non-true resting state or insufficient hyperemia. However, such discordance can also arise because FFR and NHPR reflect the hyperemic and resting physiologic states, respectively. The clinical and prognostic relevance and treatment option of these discordant lesions need further data. Recent observational studies showed that the 2-year outcomes of medically treated discordant lesions were similar to medically treated concordant negative lesions.[55-57] However, as long-term outcomes of these lesions are still unknown and more data are needed in this field, the operators should carefully determine the treatment strategy according to the patient and lesion characteristics and procedural complexity.

CORONARY PHYSIOLOGY IN PCI OPTIMIZATION

Most of the evidence supporting the clinical value of pressure-derived indexes refers to preprocedural decision-making. However, several studies have shown that, despite a good angiographic result of PCI, a substantial proportion of patients showed a post-procedural FFR <0.80 and that such suboptimal functional result is associated with poor prognosis.[58-60] In a recent patient-level data meta-

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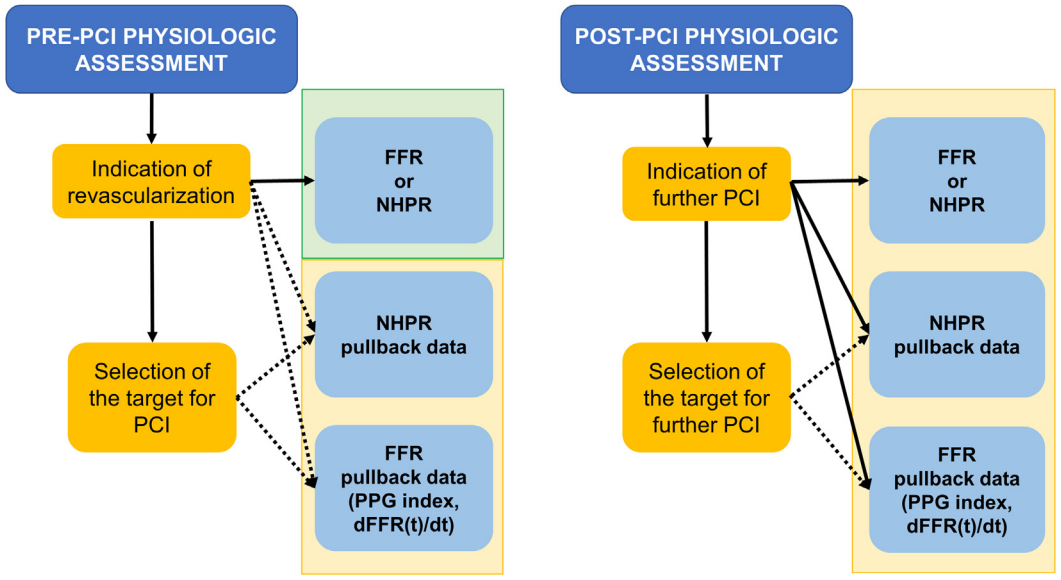
FIGURE 3 Practical Approach for PCI Optimization Using Coronary Physiology



After checking the necessity of revascularization with fractional flow reserve (FFR) or nonhyperemic pressure ratios (NHPRs), the type of lesion (focal vs diffuse) should also be considered as an indication of effective percutaneous coronary intervention (PCI) using pullback data of NHPRs and FFR. Green background indicates the current guideline recommendation. Yellow background and dotted line indicate the practically useful methods with supporting clinical data. PPG = pullback pressure gradient.

analysis of 5,277 patients, the median post-PCI FFR was 0.89, and 11.8% of analyzed vessels had a post-PCI FFR ≤0.80. Post-PCI FFR values were associated with the risk of target vessel failure and of cardiac death or MI.[59] Similarly, the DEFINE-PCI (Physiologic Assessment of Coronary Stenosis Following PCI) study showed that more than 20% of patients had suboptimal results (post-PCI iFR <0.90) after angiographically successful PCI. Among them, more than 80% of patients had residual stenosis with physiologically focal step-up of iFR, which can be corrected with PCI.[61] The conclusions that can be drawn from the discussed evidence are that a suboptimal functional result may result from inadequate planning of the intervention, low PCI precision caused by geographic miss, or inadequate removal of an obstructive epicardial lesion by PCI. On these grounds, there are 2 approaches to improve the functional results of PCI: 1) preprocedural simulation of the result or efficacy of PCI using dedicated tools;[62-65] and 2) postprocedural assessment and PCI optimization guided by physiologic tools (Figure 3).[66] These approaches are discussed in detail in the following paragraphs.

PCI OPTIMIZATION USING PRE-PCI PHYSIOLOGIC DATA. A major step forward in the use of physiology to plan PCI by simulating its effect on obstructive epicardial disease came from the development of longitudinal vessel interrogation, which is typically performed using pressure guidewire pullbacks. The value of longitudinal vessel interrogation to characterize hemodynamic patterns of coronary artery disease was described as early as 2001.[67] With the arrival of iFR, and the development of novel indexes and dedicated software for pressure pullback analysis, the interest in this diagnostic approach bloomed.[64] Outlining the longitudinal patterns of obstructive coronary atherosclerosis before PCI (eg, focal vs diffuse disease) using FFR or iFR pullback tracing is proven to be effective and might help to select the target lesion, which can achieve high physiologic gain with PCI.[63,64,68] However, when there are multiple lesions in the coronary artery, the influence of each lesion on hyperemic coronary flow generates hemodynamic crosstalk among the lesions, a situation particularly challenging when using FFR and whose mathematical solution is too cumbersome to be applied in clinical practice.[69] In this regard, NHPRs have potential advantages over FFR in the prediction of physiologic PCI results based on longitudinal vessel analysis. As NHPRs are based on resting coronary flow, which is generally constant, there is less hemodynamic

crosstalk among the lesions when compared to FFR.[70] Studies have confirmed the ability to predict the hemodynamic result of an intervention based on an iFR pullback, as well as with other NHPR.[62,64]

PCI OPTIMIZATION USING POST-PCI PHYSIOLOGIC DATA. As discussed above, a suboptimal physiologic result is observed after PCI, even in the context of physiology-driven revascularization.[66] This suboptimal result may be avoided in some cases by optimal selection of the lesion that can expect to get sufficient post-PCI physiologic gain. Suboptimal interventional procedure itself can be the reason for a suboptimal physiologic results. In this regard, additional procedures guided by post-PCI physiologic assessment can further improve the final results. The FFR-SEARCH (Fractional Flow Reserve–Stent Evaluated at Rotterdam Cardiology Hospital) study described potential mechanisms for a suboptimal post-PCI FFR using intravascular ultrasound (IVUS).[71] According to the report, IVUS identified stent underexpansion in 74%, significant residual focal lesion in the proximal or distal segment in 29% and 30%, respectively, stent malapposition in 23%, vascular spasm in 9%, lumen compromising intramural hematoma in 3%, and diffuse residual atherosclerotic disease in 8% of the cases with post-PCI FFR <0.85. Additional balloon inflation with a stepwise increase of inflation pressure further improved the post-PCI FFR and IVUS parameters.[72] Agarwal et al[58] reported that 21% of angiographically successful PCI showed low FFR (≤0.81), and subsequent intervention for those patients significantly increased FFR from 0.78 ± 0.08 to 0.87 ± 0.06 ($P < 0.0001$). In the TARGET-FFR trial, the percentage of patients with the suboptimal post-PCI result (FFR <0.80) decreased significantly by applying the additional PCI procedure compared to the conservative group.[73] However, the additional PCI procedure failed to increase the percentage of the patients who achieved the target post-PCI FFR (>0.90) compared to the conservative group.

There is still controversy over whether post-stent FFR can be considered a correctable risk factor or simply a risk marker for future events. The FFR SEARCH registry showed that the presence of underexpansion of the implanted stent by IVUS criteria was not associated with a significant drop in FFR value over the stented segment. There was only a trend toward higher pressure drops along with a higher degree of underexpansion.[71] Therefore, the final PCI result should be evaluated in a more comprehensive manner, including the information from intravascular imaging devices such as IVUS and optical coherence tomography. In addition, post-PCI FFR reflects both residual stenosis in the stented segment and residual disease burden in the target vessel, or even more, the atherosclerotic burden of the entire coronary tree of the patient.[74-76] Piroth et al[77] reported that suboptimal physiologic results after PCI could be an indicator of future clinical events in the whole coronary artery tree, including non-target vessels. Consequently, when using post-PCI physiologic assessment values in clinical practice, operators should bear in mind that PCI is a focal treatment and recognize the strengths and limitations of imaging and physiologic assessments, as well as the importance of optimal medical treatment.[78,79]

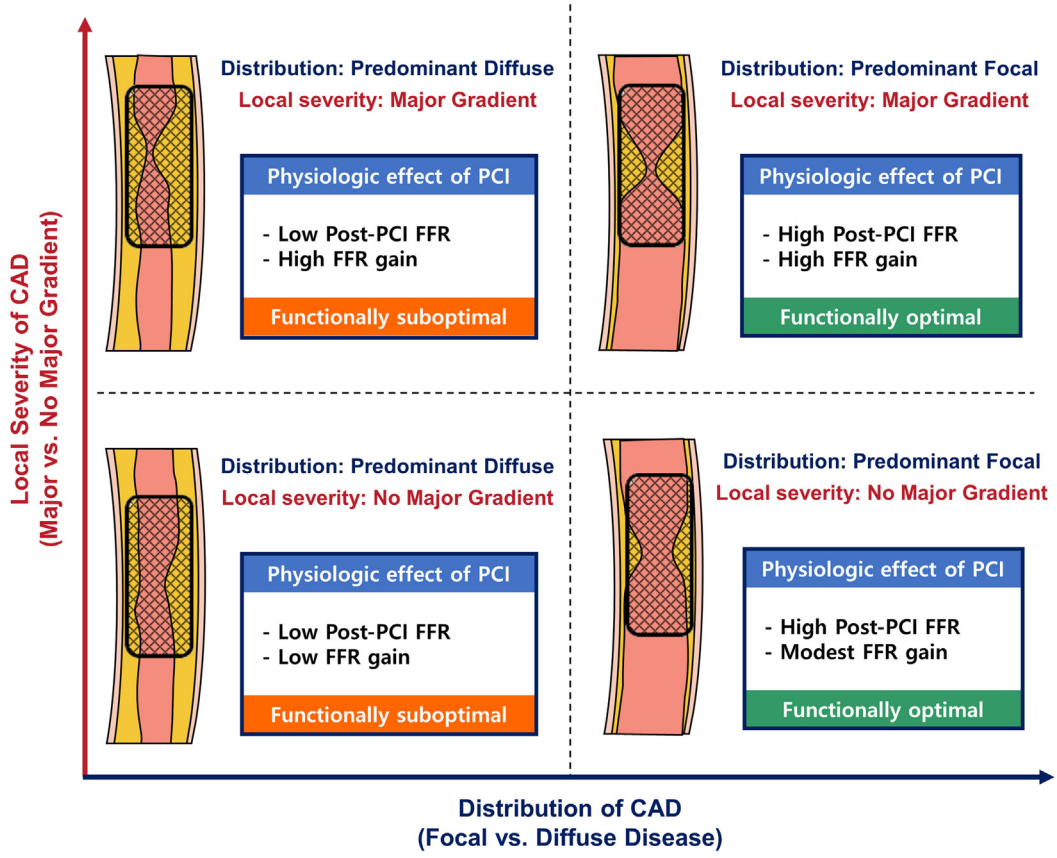
LONGITUDINAL VESSEL ANALYSIS AND PROCEDURAL PLANNING

Coronary physiologic index-guided PCI, including using FFR, NHPRs, or angiography-derived quantitative flow ratio (QFR) has shown clinical benefit when compared to imaging-guided PCI with fewer stents.[18,20,21,43,47,80,81] However, most previous randomized clinical trials did not routinely perform the post-stent physiologic assessment. As the measured values of the coronary physiologic indexes are vessel-specific rather than lesion-specific values, ischemia may remain even after optimal PCI due to the presence of residual diffuse disease in the nonstented segments.[75,76,82] This underscores the importance of longitudinal vessel analysis and procedural planning before PCI.

LONGITUDINAL VESSEL ANALYSIS FOR PHYSIOLOGIC DISEASE PATTERN. To select the optimal target for PCI, the first step is to characterize the physiologic disease patterns regarding the distribution and severity of coronary atherosclerosis. This includes assessing for focal vs diffuse disease patterns and the severity of lesions determined by the presence or absence of major pressure gradients (**Figure 4**).[68,75,76] The pressure pullback curve can provide this information, and a significant pressure step-up across a focal lesion indicates an optimal PCI target. Although further data are required, recent studies used the criteria of delta-FFR of ≥0.05 and delta-NHPR of ≥0.03 across the relatively short segment (10 to 20 mm) to define a physiologically focal lesion.[83] If the pressure step-up is gradual throughout the target vessel, local treatment with stenting is unlikely to improve the patient's physiologic and clinical prognosis.[75,76]

iFR pullback analysis with angiography coregistration has been developed to provide a simple method to determine the physiologic disease distribution in a target vessel and plan PCI

FIGURE 4 Concept of 2-Dimensional Characterization of Coronary Atherosclerotic Disease Patterns



The 2-dimensional characterization of coronary atherosclerotic disease consists of physiologic distribution (predominant focal vs diffuse) and physiologic local severity (major vs no major gradient). Physiologic distribution can be objectively assessed by PPG index. Physiologic local severity can be objectively assessed by instantaneous gradient per unit length. Modified with permission from Shin et al.[74] CAD = coronary artery disease; other abbreviations as in Figure 3.

accordingly.[62,84,85] Because of less dependency on the physiologic impact of other lesions, NHPRs can be easily used to assess the local physiologic disease severity and predict post-PCI physiologic status. Traditionally, FFR pullback tracing was used to find the primary target for PCI (lesion with major pressure step-up), and post-PCI FFR was recommended to assess the residual physiologic disease burden. Recently, novel methods using FFR pullback tracing, such as pullback pressure gradient index and instantaneous FFR gradient per unit time (dFFR(t)/dt), have been developed for objective longitudinal vessel analysis of physiologic disease patterns.[63,75] The pullback pressure gradient index can be calculated from 2 components which are the maximum FFR gradient over 20 mm and the extent of physiologic disease.[63] These indexes have shown the potential to identify coronary lesions that will result in high "FFR gain" after PCI. QFR virtual pullback or virtual planning using coronary computed tomography angiography technology can provide noninvasive quantification of these parameters.[86,87]

PROCEDURAL PLANNING FOR FUNCTIONALLY OPTIMAL PCI. The operators can select the treatment plan according to the physiologic disease patterns using the methodologies described previously. The iFR GRADIENT (Single instantaneous wave-Free Ratio Pullback Pre-Angioplasty Predicts Hemodynamic Outcome Without Wedge Pressure in Human Coronary Artery Disease) study showed that the information from pre-PCI iFR pullback significantly changed the treatment plan by modifying the number of significant lesions and total treated lesion length in 31% of interrogated vessels.[64] However, Warisawa et al[88]

TABLE 3 Comparison of Commercially Available Computational FFR Approaches Based on Imaging Data

Technology	Main Vendor	Imaging Modality	Analysis Model
FFR_{CT}	Heart Flow Inc, Redwood City, California, USA	CCTA	Offline analysis, coronary tree
CT-QFR	CtaPlus, Pulse Medical, Shanghai, China	CCTA	On-site analysis, coronary tree
cFFR	Siemens Healthcare, Forchheim, Germany	CCTA	On-site analysis, coronary tree
QFR	AngioPlus, Pulse Medical, Shanghai, China QAngio XA 3D, Medis Medical Imaging System, Leiden, the Netherlands	2 angiographic views	On-site analysis, single-vessel
FFR_{angio}	CathWorks Ldt, Kfar Saba, Israel	3 angiographic views	On-site analysis, left or right coronary tree
vFFR	CAAS workstation, Pie Medical Imaging, Maastricht, the Netherlands	2 angiographic views	On-site analysis, single-vessel
μQFR	AngioPlus Core, Pulse Medical, Shanghai, China	1 or 2 angiographic views	On-site analysis, main vessel and side branches
OFR	OctPlus, Pulse Medical, Shanghai, China	OCT pullback imaging	On-site analysis, main vessel and ostia of side branches
UFR	IvusPlus, Pulse Medical, Shanghai, China	IVUS pullback imaging	On-site analysis, main vessel and ostia of side branches

CCTA = coronary computed tomography angiography; cFFR = computed fractional flow reserve; CT-QFR = coronary computed tomography angiography-derived quantitative flow ratio; IVUS = intravascular ultrasound; OCT = optical coherence tomography; OFR = optical flow ratio; QFR = quantitative flow ratio; UFR = ultrasonic flow ratio; vFFR = vessel fractional flow reserve; μQFR = Murray law-based quantitative flow ratio; other abbreviation as in Table 1.

showed that more than 20% of operators misinterpreted the disease pattern when judged by expert consensus. Cook et al[89] evaluated the performance of artificial intelligence-based interpretation and showed that artificial intelligence interpretation was noninferior and more reproducible when compared with experts in determining both the hemodynamic appropriateness for PCI and the optimal physiologic PCI strategy. In addition to procedural planning using iFR-angiogram coregistration, NHPR's pullback analysis also enables estimation of expected post-PCI value using a simple mathematical approach as follows; predicted NHPR = pre-PCI NHPR (lowest value) + ∑intention to treat NHPR gradient(s).[62,64,84,90]

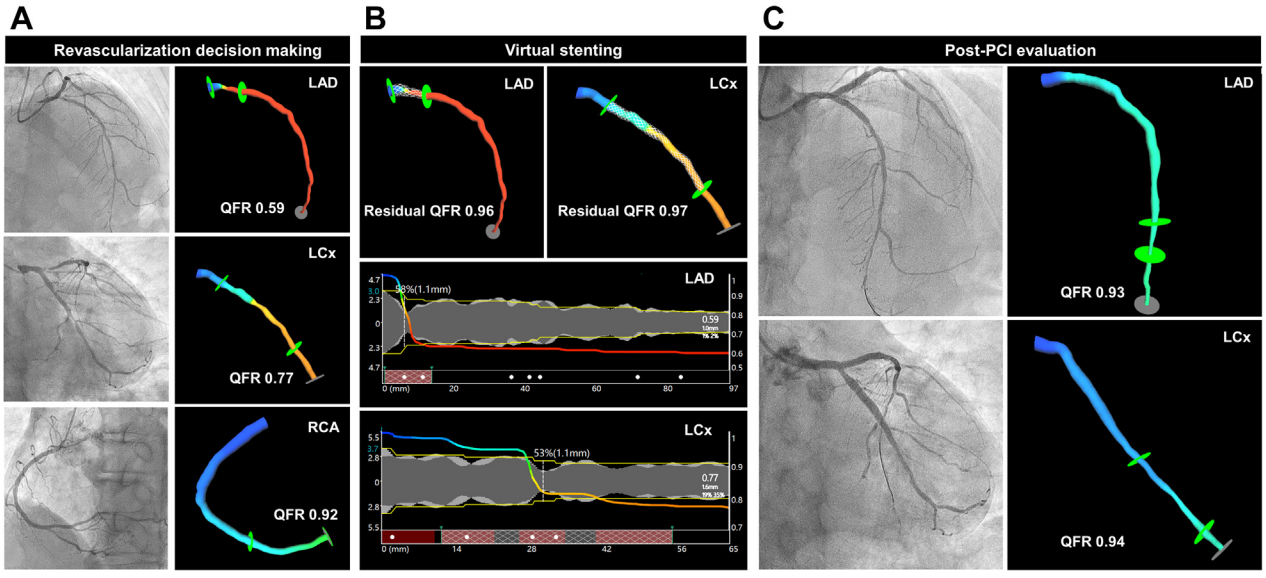
Meanwhile, the above concept has also been evaluated using less invasive tools without the use of a pressure wire. Recent studies presented the feasibility of computed tomography-derived FFR or functional coronary angiography with virtual pullback technology in procedural planning.[86,91,92] Upcoming trials in this field will provide further data on the use of these methods. The AQVA (Angio-based quantitative flow ratio virtual PCI versus conventional angio-guided PCI in the achievement of an optimal post-PCI QFR; NCT04664140) study investigators are comparing QFR-based virtual PCI with conventional angiography-guided PCI in a prospective randomized fashion. Other prospective studies are also being conducted to assess the use of the iFR coregistration system on PCI and patient clinical outcomes. The DEFINE GPS (Distal evaluation of functional performance with intravascular sensors to assess the narrowing effect: guided physiologic stenting; NCT04451044) and iLARDI (Usefulness of the use of co-registration strategy with iFR in long and/or diffuse coronary lesions; NCT04283734) investigators seek to assess the impact of iFR-angiogram coregistration system to guide PCI and influence on the numbers and lengths of stents delivered and, in the case of the DEFINE GPS trial, whether this strategy might reduce the risk of clinical events. All these studies will determine the clinical usefulness of pre-PCI planning and PCI strategy based on physiologic assessments.

WIRE-FREE IMAGE-BASED PHYSIOLOGIC ASSESSMENT

Although supported by scientific evidence and guideline recommendations, the use of wire-based physiologic evaluation, including FFR and NHPR, has remained low in most regions.[25,93] Meanwhile, wire-free image-based approaches have been developed as promising alternatives, providing physiologic assessment without the need for costly intracoronary pressure wires or hyperemic agents. These functional coronary angiography tools, which can be applied to either computed tomography-based or invasively obtained coronary angiograms (Table 3), are discussed in the following paragraphs.

CLINICAL VALIDATION OF IMAGE-BASED PHYSIOLOGIC ASSESSMENT. Most available computational physiology solutions are derived from coronary computed tomography angiography or invasive coronary angiography (Table 3); however, more recently, intracoronary imaging-derived approaches allowing the integration of coronary imaging and physiology with a single imaging catheter have been developed.[94] The level of evidence varies substantially across different computational methods, with most validations obtained by paired comparisons having invasive FFR as

FIGURE 5 QFR-Guided Revascularization Strategy Decision Making, Virtual Stenting, and Post-PCI Evaluation



(A) According to pre-PCI QFR, PCI was indicated for left anterior descending (LAD) and left circumflex (LCx) arteries. (B) For LAD, virtual stenting strategy provides optimal residual quantitative flow ratio (QFR) of 0.96. For LCx, virtual stenting strategy provides optimal residual QFR of 0.97. (C) Immediately after PCI, QFR was 0.93 for LAD and 0.94 for LCx. RCA = right coronary artery; other abbreviations as in Figure 3.

the reference standard. Overall, computational FFR techniques outperform their image-derived anatomical counterparts and show comparable diagnostic accuracies compared to invasive FFR and noninvasive imaging modalities.[95-108] Besides diagnostic performance, evidence is accumulating for the association of image-based FFR and clinical outcome.[109-113] The recent FAVOR III China study (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous InterVention in Patients With cORonary Artery Disease) and its substudies have shown that QFR-guided strategy improved 1-year and 2-year clinical outcomes compared with standard angiography guidance.[114-116]

Computational FFR techniques are feasible for use in both offline and real-time.[98,99,101,102] Accuracy of this technique could be further improved when applied to prospective datasets with strict and dedicated image acquisition protocols.[117] Intracoronary imaging, such as IVUS or optical coherence tomography-based solutions, has better reproducibility given their higher spatial resolution leading to more accurate vessel reconstruction and reduced manual corrections.[94,118,119] The use of artificial intelligence can further reduce manual interaction and improved efficiency and reproducibility.[103,107,120] Several approaches are promising for real-time physiologic assessment in the catheterization laboratory, with current methods achieving an analysis time of approximately 1 minute.[94,103]

CLINICAL APPLICATION OF IMAGE-BASED PHYSIOLOGIC ASSESSMENT. Gatekeeper to the catheterization laboratory. Accumulating evidence indicated that computed tomography-derived FFR could avoid unnecessary invasive procedures and subsequent revascularization in patients with low to intermediate risk profiles.[121-124] National Institute for Health and Care Excellence guidelines recommend using computed tomography-derived FFR for patients with stable chest pain, having the advantage of leading to a significant cost reduction by avoiding invasive testing and unnecessary treatment. Novel computations based on fluid dynamic equations have recently emerged and are anticipated to enable the onsite application of this technology.[125]

Revascularization decision making. Image-based physiologic assessment can identify lesions requiring revascularization, providing a physiologic roadmap for guiding and optimizing subsequent revascularization (Figure 5).[126] Besides the functional information, with a point-by-point functional reconstruction of the vessel and inherent coregistration with the angiographic roadmap (Supplemental Figure 1),

detailed anatomical parameters can also be provided for stent sizing and coregistration with intracoronary imaging (Supplemental Figure 2).[127-132] Coronary computed tomography angiography–derived solutions have the additional benefit of offering optimal fluoroscopic viewing angles for best visualization of coronary ostia and bifurcations.[133]

Virtual PCI planning and PCI optimization. Lower post-procedural FFR values are associated with worse clinical outcomes.[59,134,135,136] Coronary imaging combined with image-derived physiologic assessment provides detailed anatomical and functional information aiding technical aspects of PCI and prediction of post-PCI physiology.[91,137] Several techniques have shown the ability to predict post-PCI physiology based on baseline images with virtual stenting and clinical outcomes (**Figure 5**, Supplemental Figure 1).[138-142] The use of FFR derived from optical coherence tomography or IVUS has the potential advantage of providing detailed assessments of plaque morphology and accurate assessment for PCI optimization (Supplemental Figures 3 and 4).[94]

APPLICATION OF IMAGE-BASED PHYSIOLOGIC ASSESSMENT IN SPECIFIC PATIENT AND LESION SUBSETS.

Tandem stenoses. In tandem stenoses, the interpretation of hyperemic wire-based physiology is challenging due to the hemodynamic cross-talk among stenoses under hyperemia.[143] Computational solutions based on fixed-flow assumptions can be helpful in discriminating the physiologic significance of individual stenosis. In addition, virtual pressure pullback is inherently co-registered with angiographic coronary images, which is of particular interest for virtually stenting the primary stenosis (Supplemental Figure 1).[144]

Diffuse disease. The point-by-point functional distribution provided by the virtual computational pressure pullback along the vessel length can inform the functional pattern of coronary artery disease either qualitatively (eg, step-ups, progressive decline, or mixed) or quantitatively and further guide and optimize PCI (Supplemental Figure 2).[145-147]

Multivessel disease. Angiography-derived physiology is particularly appealing in the setting of multivessel disease and/or in the management of nonculprit stenoses in the setting of acute MI. QFR-derived functional SYNTAX score effectively identifies PCI beneficiaries among patients with left main or 3-vessel disease and improves procedural planning and risk stratification compared to invasive coronary angiography alone.[111,148] Computed tomography-derived FFR guided bypass surgery in patients with left main or 3-vessel disease have been shown to be feasible.[149]

Acute MI. The timing and management strategy for nonculprit lesions in patients with acute MI and multivessel disease remains an important clinical issue. The reliability of FFR in patients with a large MI is still controversial because maximal hyperemia might not be achieved due to microvascular disturbances. Retrospective data showed the feasibility and diagnostic accuracy of QFR assessment of nonculprit lesions during the index vs staged phase (Supplemental Figure 4).[150-153] Pilot randomized trials showed that QFR-guided complete revascularization of nonculprit lesions in the acute phase resulted in reduced major adverse cardiovascular events compared to the culprit-only treatment.[154,155] Intracoronary imaging-derived solutions for the assessment of the culprit vessel in patients with acute MI are feasible and warrant further validation.[156]

Bifurcation lesions. One of the drawbacks of computational physiology is the inadequacy in assessing the functional significance of side branches in bifurcation lesions (**Table 3**). Recently, QFR based on a single angiographic view using Murray law–derived step-down reference lumen across bifurcations has been developed for this purpose and can be applied in the bifurcation lesions both before and after PCI (Supplemental Figure 5).[157] Intracoronary imaging-based solutions might be promising given detailed morphological and physiologic information in patients with bifurcation lesions, but further investigations are warranted in this complex clinical setting.

In-stent restenosis. Recent datasets indicated the prognostic value of angiography-derived FFR after treatment of in-stent restenosis lesions by drug-coated balloon angioplasty.[158-160] Intracoronary imaging-derived FFR is particularly useful in this setting as it provides information on the morphological mechanisms related to stent failure (under-expansion, late-acquired malapposition, or uncovered struts) in addition to the physiologic relevance of the lesions[141]; it also helps optimize PCI technique in these cases.

FUTURE PERSPECTIVES

Functional assessment of coronary stenosis could be further combined with plaque burden, composition, and biomechanics from imaging to better predict clinical outcome as the adverse cardiovascular events may also occur in patients with nonobstructive coronary artery disease.[161] Automatic detection and quantification of high-risk plaque features combined

with computed physiology may refine the diagnostic strategy and will be investigated in future studies.[162] Further randomized controlled trials are needed to inform about the applicability of computational physiology to guide clinical decision-making as well as cost effectiveness. Computational physiology is anticipated to be incorporated into routine clinical practice to identify flow-limiting coronary stenosis, define the appropriate strategy of revascularization, and allow its procedural optimization.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work is supported by the grant from the Patient-Centered Clinical Research Coordinating Center (grant number: HC19C0305). Dr Koo has received institutional research grants from Abbott Vascular, Boston Scientific, Philips, and HeartFlow. Dr Joo Myung Lee has received institutional research grants from Abbott Vascular, Boston Scientific, Philips Volcano, Terumo Corporation, Zoll Medical, and Donga-ST. Dr Seung Hun Lee has received an institutional research grant from Abbott Vascular. Dr Tu is a co-founder of Pulse Medical and has received institutional research grants from Pulse Medical. Dr Nam has received an institutional research grant from Abbott Vascular. Dr Yong has received honoraria from Abbott Vascular; and has received institutional research grants and support from Abbott Vascular and Philips. Dr Harding has received proctoring fees/speaker honoraria from Abbott Vascular, Boston Scientific, Medtronic, and Terumo Medical. Dr Hu has received an institutional research grant from Boston Scientific. Dr Wang has received an institutional research grant from Boston Scientific. Dr Fearon has received institutional research support from Abbott, Boston Scientific, and Medtronic; has received consulting fees from CathWorks and Siemens; and has stock options with HeartFlow. Dr Escaned has received personal fees as speaker or advisory board member from Abbott, Boston Scientific, Medis, RainMed, and Philips; he also reports joint ownership of angio-IMR patent. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS Asia-Pacific, coronary artery disease, coronary physiologic assessment

APPENDIX For a list of Working Members of Asia-Pacific Expert Consensus Document and supplemental figures, please see the online version of this paper.